REMARKS

Claims 13, 29, and 47 have been amended to correct typographical errors. Claims 4, 7, 38, and 41 have been amended to more clearly define the claimed subject matter. Claims 57 and 58 have been cancelled. New claims 59 and 60 have been added. Claims 1, 21, 35, and 59 are independent.

Election

Applicants affirm election of Group I, claims 1-56. Applicants affirm the election of species CdSe as a Group II-VI compound as the first semiconductor material, ZnS as a Group II-VI compound as the second semiconductor material, and polypeptide as the macromolecule.

Objections

The Examiner has objected to claims 3, 4, 7, 23, 37, 38 and 41 because the claims recite non-elected semiconductor materials. See page 4 of the Office Action. Applicants note that these claims read on the elected species and should be maintained in this application.

Obviousness-type Double Patenting Rejections

The '610 Patent

Claims 1-9, 11-13, 15, 16, 35-43, 45-47, 49 and 50 have been rejected by the Examiner under the judicially created doctrine of obviousness-type double patenting over claims 1-10, 16-18, 29-32, 37, 38 and 45-57 of U.S. Patent No. 6,306,610 ("the '610 patent"). See pages 4-6 of the Office Action.

Applicants have discovered ionic conjugates and methods of forming ionic conjugates. The ionic conjugates include an inorganic particle, a linking group which has a distal end and a proximal end, the distal end being bound to an outer surface of the inorganic particle and the proximal end including a first charged or ionizable moiety, and a macromolecule having a second charged or ionizable moiety, wherein the first and second charged or ionizable moieties

electrostatically associate the inorganic particle with the macromolecule to form an ionic conjugate. See independent claims 1, 21, 35, and 59.

Claims 1-10, 16-18, 29-32, 37, 38 and 45-57 of the '610 patent are directed to compositions including a first member of a binding pair linked to a semiconductor nanocrystal. The '610 patent describes a binding pair at column 6, lines 51-61. Specifically, "the term 'binding pair' refers [to] first and second molecules that specifically bind to each other. 'Specific binding' of the first member of the binding pair to the second member of the binding pair in a sample is evidenced by the binding of the first member to the second member, or vice versa, with greater affinity and specificity than to other components in the sample."

The claims of the '610 patent do not describe a linking group having a proximal end including a first charged or ionizable moiety, and a macromolecule having a second charged or ionizable moiety, wherein the first and second charged or ionizable moieties electrostatically associate. The electrostatic association is not "specific binding" of the kind described in the claims of the '610 patent.

Claims 1-10, 16-18, 29-32, 37, 38 and 45-57 of the '610 patent do not teach, suggest, or motivate a person skilled in the art to make a composition that includes an inorganic particle, a linking group bound to an outer surface of the inorganic particle and including a first charged or ionizable moiety, and a macromolecule having a second charged or ionizable moiety, wherein the first and second charged or ionizable moieties electrostatically associate the inorganic particle with the macromolecule to form an ionic conjugate. Applicants respectfully request reconsideration and withdrawal of this rejection.

The '144 Patent

Claims 1-5, 8, 9, 11-12, 15, 16, 35-39, 42, 43, 45-46, 49 and 50 have been rejected by the Examiner under the judicially created doctrine of obviousness-type double patenting over claims 1-72 of U.S. Patent No. 6,326,144 ("the '144 patent"). See pages 6-7 of the Office Action.

The Examiner asserts that claims 1-72 of the '144 patent "disclose[] a composition comprising a compound; a semiconductor nanocrystal linked to the compound by a ligand of the formula $H_zX((CH_2)_nCO_2H)_y$, where the compound has an affinity for a biological target, and the

affinity of the compound to the biological target can be hydrophilic or electrostatic attraction and wherein the compound can be a protein, a peptide or a nucleic acid." See page 6 of the Office Action. Applicants respectfully disagree. The claims of the '144 patent teach only a compound having an affinity for a biological target that is linked to a semiconductor nanocrystal by a ligand of the formula $H_zX((CH_2)_nCO_2H)_y$. They do not teach a person of ordinary skill in the art to use a linking group having a proximal end including a first charged or ionizable moiety to associate an inorganic particle with a macromolecule having a second charged or ionizable moiety. Claims 1-72 of the '144 patent do not teach or suggest a composition that includes an inorganic particle, a linking group bound to an outer surface of the inorganic particle and including a first charged or ionizable moiety, and a macromolecule having a second charged or ionizable moiety, wherein the first and second charged or ionizable moieties electrostatically associate the inorganic particle with the macromolecule to form an ionic conjugate.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-56 under 35 U.S.C. § 112, first paragraph, for lack of enablement. See pages 7-10 of the Office Action. In particular, the Examiner states "[t]he specification... only discloses cursory conclusions without data supporting the findings, which states that an ionic conjugate forms through self-assembly in which inorganic particles electrostatically associate with at least one macromolecule."

When a rejection is based on the contention that the disclosure is not commensurate in scope with the protection sought, "it is incumbent upon the Patent and Trademark Office... to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with **acceptable evidence or reasoning** which is inconsistent with the contested statement (emphasis added)." In re Marzocchi, 169 U.S.P.Q. 367, 369-70 (CCPA 1971). The Examiner has presented no evidence or reasoning that explains why the disclosure is not enabling.

With regard to the breadth of the claims, the Examiner contends that "[t]he breath [sic] of the claims is broad and encompasses unspecified variants regarding inorganic particles and

macromolecules in the composition, which are not adequately described or demonstrated in the specification."

Inorganic particles are described clearly, for example at pages 9-10. Additional description of semiconducting nanoparticles and their preparation is presented on pages 10-14. The macromolecule is described, for example, in the specification at page 14, lines 18-27. The claims are commensurate in scope with the teachings of the specification.

A statement of generic operability in the specification must be accepted as accurate in the absence of proof to the contrary. Wettstein v. Campbell, 139 U.S.P.Q. 341, 343 (BOPI 1962). The Examiner has not sustained the burden of proof as to inoperability of the generic claims (i.e. claims 1, 21, and 35). Moreover, even if some of the claimed species were inoperative, the generic claims are not necessarily invalid, since it is well established that "[i]t is not a function of the claims to specifically exclude... possible inoperative substances...." In re Dinh-Nguyen, 181 U.S.P.Q. 46, 48 (CCPA 1974).

Furthermore, a claim is not necessarily invalid, even if supported by minimal evidence of reduction to practice. For example, a patent covering claims to the process of using monoclonal antibodies in sandwich assays was upheld by the Federal Circuit. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (CAFC 1986). Even though data on **only one** antigen are presented in that patent, claims directed to a method of quantifying **all** antigenic substances were nonetheless held enabled. Id., at 94.

With regard to working examples, the Examiner has noted that the specification provides two working examples of an ionic conjugate of "semiconductor nanoparticles (CdSe-ZnS) with Maltose binding protein (MBP)-leucine zipper fusion protein or with protein G-leucine zipper fusion protein (pages 22-29)." See page 9 of the Office Action.

It is not necessary to provide a working example for every embodiment encompassed by the claims. As pointed out by the Court of Customs and Patent Appeals in a decision involving chemical claims, "appellants [here, applicants] are **not** required to disclose every species encompassed by their claims even in an unpredictable art" (emphasis original). In re Angstadt, 537 F.2d 498, 503 (CCPA 1976). Furthermore, claim 21 recites a composition including an inorganic particle, a linking group, and a fusion protein. Claim 59 recites a method of forming

an ionic conjugate that includes providing a semiconductor nanocrystal including a linking group including a first charged or ionizable moiety, and contacting a fusion protein having a second charged or ionizable moiety with the semiconductor nanocrystal, to form an ionic conjugate. Claims 21 and 59 and the claims that depend from them are clearly enabled in light of the working examples (see the specification at pages 22-29).

The Examiner states regarding the state of the prior art and skill of those in the art that "the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide more teachings on the make and use of ionic conjugates containing various inorganic particles and various macromolecules to be considered enabling for the claimed method." See the Office Action at page 9.

Applicants assert that the disclosure enables of the full scope of the claims. There is no 'omitted description'.

With regard to predictability or unpredictability, the Examiner contends that "the specification does not provide the make/use of ionic conjugates containing various inorganic particles and various macromolecules, the invention is highly unpredictable regarding the effects of various ionic conjugates." See page 9 of the Office Action.

The effects of the ionic conjugates, and the predictability of those effects, are not relevant to the question of enablement.

With respect to the amount of direction or guidance / quantity of experimentation necessary, the Examiner states that despite the inclusion of two working examples, "the specification has not demonstrate [sic] the making and use of various ionic conjugates containing different inorganic particles and different macromolecules." See the Office Action at page 10.

The working examples are exactly that: examples. As discussed above, it is not necessary to provide a working example for every embodiment encompassed by the claims. The Examiner has not shown that the specification provides insufficient direction or guidance to enable a person skilled in the art.

Regarding the nature of the invention, the Examiner again indicates that the specification does not provide sufficient teachings to enable the making and use of various ionic conjugates. See the Office Action at page 10. As noted above, Applicants assert that the disclosure enables

of the full scope of the claims. Indeed, the Examiner has not indicated why the disclosure is not enabling.

The claims are enabled. Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 4-7 and 38-41 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner contends that the term "mixtures thereof" is inappropriate use of open language in a Markush group. Claims 4, 7, 38 and 41 have been amended so as to more clearly define the scope of the claims. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

Mirkin

Claims 1-5, 8-12, 15, 35-39, 42-46 and 49 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Mirkin *et al.*, WO 98/04740 ("Mirkin"). See page 12 of the Office Action. Applicants respectfully disagree.

The Examiner states that Mirkin teaches "a method of detecting nucleic acids by contacting a nucleic acid with one or more types of nanoparticles having oligonucleotides attached thereto, where the nucleic acid has at least two portions and the oligonucleotides on the nanoparticles have a sequence complementary to the sequence of one of the portions of the nucleic acid... under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with the nucleic acid." See the Office Action at page 12.

Applicants have discovered ionic conjugates and methods of forming ionic conjugates. The ionic conjugates include an inorganic particle, a linking group which has a distal end and a proximal end, the distal end being bound to an outer surface of the inorganic particle and the proximal end including a first charged or ionizable moiety, and a macromolecule having a second charged or ionizable moiety, wherein the first and second charged or ionizable moieties

electrostatically associate the inorganic particle with the macromolecule to form an ionic conjugate. See independent claims 1, 21, 35, and 59.

Mirkin describes the attachment of oligonucleotides to nanoparticles at pages 21-22. The attachments described by Mirkin include: oligonucleotides functionalized at their 3'- or 5'-termini with alkanethiols for attachment to gold nanoparticles; phosphorothioates for the binding of oligonucleotides-phosphorothioates to gold surfaces; substituted alkylsiloxanes for binding of oligonucleotides to silica and glass surfaces; biotin-labeled oligonucleotides that attach to streptavidin-gold conjugates; disulfides on gold; carboxylic acids on aluminum, copper, platinum, or silica; aromatic ring compounds on platinum; sulfolanes, sulfoxides and other functionalized solvents on platinum; isonitriles on platinum; silanes on silica; and aromatic carboxylic acids, aldehydes, alcohols and methoxy groups on titanium dioxide and silica.

The attachments described by Mirkin are ligands that bind to a nanoparticle, the ligands being covalently attached to an oligonucleotide. None of the attachments is a linking group having a first charged or ionizable moiety that electrostatically associates with a second charged or ionizable moiety of a macromolecule.

The Examiner further states that Mirkin teaches "nanoparticles [that] include metal such as silver (claims 10 and 44) and semiconductor materials, e.g., CdSe and CdS (page 19, lines 24-34; claims 2-5 and 37-39), and each nanoparticles has a plurality of oligonucleotides attached to it, thus each nanoparticle-oligonucleotide conjugate can bind to a plurality of nucleic acids having complementary sequence (page 22, lines 30-34; claims 8, 9, 43 and 43)." The binding of oligonucleotides to nucleic acids of complementary sequence does not involved electrostatic association.

Mirkin does not teach a linking group including a first charged or ionizable moiety, and a macromolecule having a second charged or ionizable moiety, wherein the first and second charged or ionizable moieties electrostatically associate. Nor does Mirkin teach a method of forming an ionic conjugate that includes such a linking group. Therefore, Mirkin does not anticipate claims 1-5, 8-12, 15, 35-39, 42-46 and 49.

The '610 Patent

Claims 1-9, 11-13, 15, 16, 35-43, 45-47, 49 and 50 have been rejected under 35 U.S.C. § 102(e) as being anticipated by the '610 patent. See pages 12-13 of the Office Action.

As described by the Examiner, the '610 patent teaches "a fluorescent semiconductor nanocrystal having an overcoating layer, associated with a compound that has affinity and can physically interact with a biological target... wherein the affinity is hydrophilic, ionic or electrostatic attraction... and wherein the compound... has the structural formula (I), (II), (III), or (IV)."

The compounds of the '610 patent having formula I, II, III, or IV, are described as water solublizing compounds. See the '610 patent at column 16, lines 11-13. These compounds do not have a first charged or ionizable moiety that electrostatically associates with a second charged or ionizable moiety belonging to a macromolecule. Indeed, the compounds of the '610 patent having formula I, II, III, or IV, are water solublizing compounds. The '610 patent does not describe these compounds electrostatically associating with a macromolecule.

The '610 patent does not teach a linking group including a first charged or ionizable moiety, and a macromolecule having a second charged or ionizable moiety, wherein the first and second charged or ionizable moieties electrostatically associate.

The '144 Patent

Claims 1-5, 8, 9, 11-12, 15, 16, 35-39, 42, 43, 45-46, 49 and 50 have been rejected under 35 U.S.C. § 102(e) as being anticipated by the '144 patent.

As described by the Examiner, the '144 patent teaches "a fluorescent semiconductor nanocrystal having an overcoating layer, associated with a compound that has affinity and can physically interact with a biological target... wherein the affinity is hydrophilic, ionic or electrostatic attraction... and wherein the compound... has the structural formula $H_zX((CH_2)_nCO_2H)_y$." See the Office Action at page 13.

The compounds of the '144 patent having the structural formula $H_zX((CH_2)_nCO_2H)_y$ are described as water solublizing compounds. See the '144 patent at column 7, line 66 through column 8, line 59. These compounds do not have a first charged or ionizable moiety that electrostatically associates with a second charged or ionizable moiety belonging to a

macromolecule. The '144 patent does not teach a linking group including a first charged or ionizable moiety, and a macromolecule having a second charged or ionizable moiety, wherein the first and second charged or ionizable moieties electrostatically associate.

Applicants respectfully request that all rejections under 35 U.S.C. § 102 be withdrawn.

New Claims

New claims 59 and 60 relate to a method of forming an ionic conjugate that includes providing a semiconductor nanocrystal including a linking group having a first charged or ionizable moiety, and contacting a fusion protein having a second charged or ionizable moiety with the semiconductor nanocrystal. The new claims are patentable over the cited references.

CONCLUSION

Applicants ask that all claims be allowed. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 11-7-03

Harold H. Fox
Reg. No. 41,498

Fish & Richardson P.C.
1425 K Street, N.W.
11th Floor
Washington, DC 20005-3500
Telephone: (202) 783-5070
Facsimile: (202) 783-2331